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Client Reference: 204704/JND/RD/nlb

OFFICIAL

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re PATENT APPLICATION of:
FRANK LARSEN ET AL.

Confirmation No: 4584

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AUG 18 2004

Application No.: 09/890,567

Group Art Unit: 1634

Filed: April 2, 2002

Examiner: C.J. Myers

Title: DETECTING TELOMERASE ACTIVITY

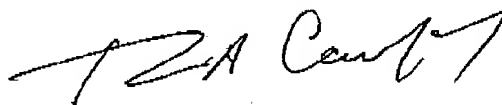
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

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Petition for Extension of Time
Response to Restriction Requirement

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(Certification of Facsimile Transmission—page 1)

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RESPONSE TO RESTRICTION REQUIREMENT

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Sir:

This is in response to the restriction requirement dated February 18, 2004, wherein the examiner alleged that pending claims 34-65 were directed to patentably distinct species of the claimed invention and required restriction. Reconsideration is requested in view of the following remarks.

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I. REMARKS

In response to the examiner's restriction requirement, the applicants have set forth below an election with traverse. This response is timely filed as it is accompanied by a petition for extension of time in the fifth month with the required fee. Should the Patent Office determine that additional fees are required for consideration of this response, permission is hereby granted to charge such fees to Deposit Account No. 033975. Any overpayments should be credited to the same account.

Restriction

Citing U.S.C. §121, the examiner alleged that claims 34-65 are directed to the following two distinct inventions:

Group I. Claims 34-50 and 61-65 (claims directed to methods for cancer diagnosis and methods for detecting telomerase activity); and

Group II. Claims 51-60 (claims directed to a kit comprising a solid phase for binding telomerase and one or more components for assaying telomerase activity).

Election

The applicants hereby elect the claims of Group I, as directed to methods for cancer diagnosis and methods for detecting telomerase activity, *with traverse*.

Traversal Arguments-Restriction of Claims 34-65 are Improper

Groups I and II

The applicants request examination of Groups I-II together because the inventions cited by the examiner as representative of such groups are related inventions and examination of all claims comprising these groups would not constitute an undue burden to the Patent Office. We note that the examiner asserts a unity of invention only when there is a technical relationship amongst those inventions involving one or more of the same or corresponding technical features. The examiner further asserted the idea that a "special technical feature" refers to those technical features that define a contribution which each of the claimed inventions makes over the prior art. The examiner alleged the linking technical feature of a solid phase for binding telomerase wherein the solid phase comprises a reagent for binding

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target whole cells, such as an affiant that is specific for epithelial cells, does not constitute a contribution over the prior art. The examiner asserted that in view of the teachings of Hardingham *et al.*, *Molecular Medicine* 1:789-794 (1995) (hereafter Hardingham *et al.*), it would have been obvious to one of ordinary skill in the art at the time the invention was made to have generated kits comprising a solid phase for binding telomerase wherein the solid phase comprises a reagent for binding epithelial cells and reagents of DNA polymerase and/or dNTPs (reagents for assaying for telomerase activity) in order to detect tumor cells. The examiner concluded there is no special technical feature linking the recited groups to fulfill the requirement for unity of invention.

The applicants respectfully submit that the special technical feature between Groups I and II is not only (1) the solid phase that unexpectedly binds telomerase wherein the solid phase comprises a reagent (e.g., antibodies) for binding target whole cells, but also (2) a telomerase specific oligonucleotide primer, which is utilized to detect telomerase activity via the catalytic component hTERT (human telomerase reverse transcriptase) of a telomerase enzyme.

With regard to the technical feature of a solid phase binding telomerase, Hardingham *et al.* do not teach or suggest that their immunomagnetic beads (similarly used to isolate epithelial cells from the blood) would be capable of binding telomerase. Specifically, Hardingham *et al.* did not teach or suggest that telomerase, or for that matter any protein components, would bind non-specifically to the immunomagnetic beads and allow one to assay for telomerase activity directly from the beads.

Binding an active telomerase enzymatic protein on the immunomagnetic beads was also not inherently known in the art. As described in Example 6, there were no known antibodies to the catalytic telomerase component hTERT at the time of filing, yet the hTERT protein component of telomerase unexpectedly bound in a non-specific manner to the immunomagnetic beads even in the presence of lysis buffer used to lyse the bound epithelial cells (see Example 1; Example 6). The specific affinity of telomerase proteins to the beads would not be an inherent property of the immunomagnetic beads used in Hardingham *et al.* because Hardingham *et al.* did not know of the specific limitation that telomerase could bind non-specifically to immunomagnetic beads, which were intended to only bind epithelial cells in the blood (See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986)).¹

¹ The applicants case is similar to the *Hybritech Inc. v. Monoclonal Antibodies*. In *Hybritech Inc.*, the trial court committed clear error in finding that claims to a "sandwich assay" using monoclonal antibodies that called for using antibodies with a certain antigen affinity were anticipated by a prior invention by another.

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A second special technical feature between the claims of Group I and Group II, which was neither taught nor suggested by Hardingham *et al.*, is the actual components of the telomerase assay. Specifically, the synthetic oligonucleotide primer used in the TRAP assay (telomeric repeat amplification protocol) is specific for human telomerase sequences wherein the oligonucleotide is elongated via the human telomerase reverse transcriptase component. The applicants have shown that telomerase, and more specifically, the reverse transcriptase component of telomerase, not only binds in a non-specific manner to immunomagnetic beads in a lysis buffer, but also elongates single stranded oligonucleotides by RNA-templated DNA synthesis. Hardingham *et al.* simply teach the use of PCR components (two primers, dNTPs, Taq polymerase) to detect the *k-ras* gene and does not contain the specific telomerase specific primer. In contrast, the applicants' method and kit are the first to utilize the reverse transcription property of telomerase in order to elongate the telomerase specific oligonucleotide (i.e., use telomerase specific primer), and then use PCR components (i.e., TRAP primer mix, dNTP mix, Taq polymerase) to amplify the elongated oligonucleotide sequence for a determination of telomerase activity. Accordingly, the applicants' invention utilizes one primer for telomerase elongation, and then two other primers for Taq polymerase amplification of the elongated oligonucleotide sequence.

Thus, even though Hardingham *et al.* used immunomagnetic beads to isolate epithelial cells in the blood, and then used PCR to detect mutations in the *k-ras* gene, Hardingham *et al.* did not teach or suggest using a solid phase capable of binding telomerase and an assay utilizing the reverse transcriptase component of telomerase. The reverse transcriptase component of telomerase is absolutely required to determine telomerase activity during cellular immortalization and tumor progression. The claims of Group II are directed to a kit, wherein the kit uses a solid phase for binding telomerase and a telomerase specific primer for detecting telomerase activity (See pg. 6, lines 18-21; pg. 8, lines 3-22; pg. 30, lines 12-19, pg 13a, lines 3-5; pg. 14, lines 1-3; Example 1; and pg. 35, lines 15-21). These special technical features contribute both to the method claims of Group I and the kit claims of Group II, which utilize the methods of Group I. Accordingly, Group I and II relate to a single inventive concept that is distinguishable and non-obvious over the prior art. In view of the foregoing, the applicants respectfully request that the restriction requirement with respect to Groups I and II be withdrawn and these groups be examined simultaneously.

While that invention did involve a sandwich assay, the prior invention did not know the affinities of the antibodies that they used and the specific affinity limitation could not be found in their work.

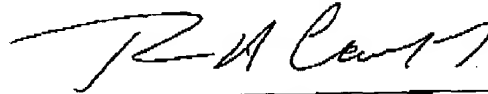
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II. CONCLUSION

In view of the foregoing, the applicants submit that they have fully and properly responded to the outstanding restriction requirement and request that substantive examination should be undertaken. Should the examiner have any questions or comments regarding this response or the application, the examiner is urged to contact the undersigned at the number indicated.

Respectfully submitted,

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